Acad. Sci. USA, 96, 6235-6240, May 1999). Applicants address the rejections in the remarks set forth below.

Rejections Under 35 U.S.C. §112

Claims 1, 17, 18 and 21 are rejected under 35 U.S.C. §112, first paragraph as non-enabling. More particularly, the Examiner asserts that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims without undue experimentation. While being enabling for a method of modulating growth-factor activation comprising contacting a cell which contains a growth-factor receptor capable of being activated with a modulator of G-protein mediated signal transduction in *in vitro*, the Examiner asserts that the specification does not reasonably provide enablement for: (1) a method for modulating growth-factor activation in an organism comprising a cell which contains a growth-factor receptor capable of being activated with a modulator of G-protein mediated signal transduction; and (2) using a method for modulating growth-factor activation comprising contacting a cell which contains a growth-factor capable of being activated with a modulator of G-protein mediated signal transduction in the prevention or treatment of disorders associated with a disturbed growth factor receptor activation such as cancer or asthma as described in claims 17, 18 and 21.

Applicant note that no animal model data are available thus far. Applicant respectfully disagrees with the examiner's assertion that lack of animal model data precludes reasonable interpretation and extrapolation of *in vitro* results to *in vivo* results.

The present application describes the biological action mechanism as well as possible applications in the case of various diseases in detail. For example, Applicant directs the Examiner's attention to page 3, lines 18-29 of the present application wherein Applicant explains the well-known connection between the modulation of G-protein mediated signal transduction and the prevention and treatment of medical disorders. Furthermore, actual *in vitro* activity is shown in the Examples and the specification contains numerous references available to the skilled artisan demonstrates how to use said *in vitro* results to carry out the invention *in vivo*. For example, Page 4, line 20 through page 5, line 21 cites and describes the process for determining effective therapeutic doses from *in vitro* data. Thus, since the present specification provides all of the details required for carrying out the invention, the Applicants respectfully request that the rejection of claims 1, 17, 18 and 21, under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejections Under 35 U.S.C. §102(b)

Claims 1-7 are rejected under 35 U.S.C. §102 as anticipated by Daub et al. (EMBO.J. 16, 7032-7044, December 1997).

More particularly, the Examiner notes that Daub et al. does not show that the activation of EGF receptor was mediated by extracellular domain as described in the limitation of Claim 1 of the present invention. However, the Examiner asserts that in absence of convincing evidence to the contrary, the limitation of Claim 1 is considered as inherent to the reference taught by Daub et al. since the method taught by Daub et

al. could contain a transactivated EGF receptor protein-couple receptor, even though Daub et al. did not known that the process was mediated by an extracellular domain.

Applicant respectfully disagrees with the Examiner's rejection of the present application under 35 U.S.C. §102 as anticipated by Daub *et al.*, (EMBO. J. 16, 7032-7044, December 1997). Daub et al. explicitly describes an *intra*cellular mechanism, namely a ligand-independent mechanism. Based on this explicit description, Daub et al. contains examples of testing using various possible *intra*cellular mediators. In direct opposition to Daub, the present invention is based on the holding that the EGFR transactivation proceeds through a ligand-dependent mechanism via the *extra*cellular domain. This feature is found explicitly in Claim 1 of the present invention. Contrary to the Examiner's assertions, Daub et al. cannot anticipate the present invention implicitly or inherently. Daub et al refers to an *intra*cellular mechanism but to no *extra*cellular mechanism. The Examiner's arguments on page 8 of the Office Action assume knowledge not present at the time this application was filed. The skilled artisan who reads Daub et al. without knowing the present invention would have been explicitly referred to an *intra*cellular mechanism and thus away from the present invention.

Furthermore, the subject matter of the present invention, namely that EGFR transactivation proceeds ligand-dependent via the extracellular domain, leads to three new intervention points in mitogenic GPCR signaling which can be used pharmaceutically. These three new intervention points are metalloproteases, EGF-like ligands and the extracellular EGFR domain. Before the present application was filed, one skilled in the art could not gather these three new intervention points from the prior

art, and therefore one skilled in the art could not surmise that these three intervention points might be intervention points.

Rejections Under 35 U.S.C. §102(a)

Claims 1, 3-16, 19 and 20 are rejected under 35 U.S.C. §102(a) as anticipated by Dong et al. (Proc. Natl. Acad. Sci. USA, 96, 6235-6240, May 1999).

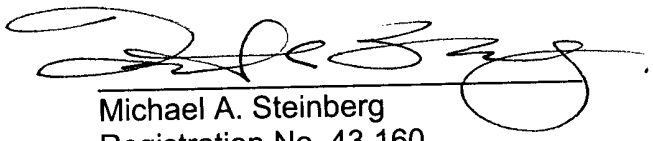
More particularly, the Examiner asserts that Dong et al teaches metalloprotease-mediated ligand release autocrine signaling through the epidermal growth factor receptor. The Examiner further asserts that Daub et al. teaches all limitations recited by claims 1, 3-16, 19 and 20.

Applicant respectfully disagrees with Examiner's assertions. Dong et al. does not anticipate the subject matter of the present invention. Dong et al. teaches only a connection between EGF ligands and the EGF receptor. In contrast, the present invention discloses the involvement of metalloproteases, EGF-like ligands and EGFR in mitogenic signal transduction of G-protein-coupled receptors. The involvement of metalloproteases, EGF-like ligands and EGFR in mitogenic signal transduction of G-protein-couple reactions as disclosed in the present application is not taught by Dong et al. This mere connection between EGF ligands and the EGF receptor, as in the case of Dong, does not at all allow itself to provide a pharmaceutical application for GPCR signaling. Pharmaceutical applicability is provided *only* by the invention described in the present application.

Applicants believe that a complete response has been made to the Office Action dated May 18, 2001, and that the application stands in condition for allowance. Such action is respectfully requested. If the Examiner has questions regarding the application or the contents of this response, he is invited to contact Michael Steinberg at (202) 857-6293.

Please charge any fee deficiency or credit any overpayment to Deposit Account No. 01-2300.

Respectfully submitted,



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